**Universidade de Lisboa**

**Faculdade de Farmácia**


# Nosocomial Infections related to Medical Devices

**Joana Maria Oliveira Brito**

**Mestrado Integrado em Ciências Farmacêuticas**

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# Nosocomial Infections related to Medical Devices

**Joana Maria Oliveira Brito**

**Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia**

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# Abstract

Hospital acquired infections are the fourth leading cause of disease in industrialised countries and the use of medical devices represents one of the most important risk factors to predispose patients to these infections. A substantial amount of common devices, like catheters and endotracheal tubes are used in hospital environment, and the insertion of more specialized medical devices, like prostheses or pacemakers and cardioverter-defibrillators is performed regularly. Once these devices are inserted, colonized by microorganisms, and covered by a biofilm, the chance of an infection is massive. But despite the risks, their utilization and application has increased over the years, so it is important to understand what are the major causative pathogens, their infection mechanism and how to battle them.

The aim of the present work is to review the current literature regarding the pathogenesis of device-associated nosocomial infections, and to identify strategies of management and prevention for these infections.



**Keywords:** hospital-acquired infections, medical device associated infections, pathogenesis, management, prevention

# Resumo

As infeções nosocomiais são a quarta principal causa de doença nos países industrializados e a utilização de dispositivos médicos é um dos fatores de risco associados mais importantes. No ambiente hospitalar são utilizados uma quantidade substancial de dispositivos comuns, como cateteres e tubos endotraqueais, e a inserção de dispositivos médicos mais especializados, como próteses ou pacemakers e cardioversores desfibrilhadores, é realizada regularmente. Assim que esses dispositivos são inseridos, colonizados por microrganismos e cobertos por um biofilme, a probabilidade do desenvolvimento de uma infeção é enorme. Apesar dos riscos, a sua utilização e aplicação aumentaram ao longo dos anos, por isso é importante entender quais são os principais agentes patogénicos responsáveis, o seu mecanismo de infeção e como combate-los.

O objetivo do presente trabalho é rever a literatura quanto à patogénese das infeções nosocomiais associadas aos dispositivos médicos e identificar estratégias de tratamento e prevenção para as mesmas.

**Palavras-chave:** infeções nosocomiais, infecções associadas a dispositivos médicos, patogénese, tratamento, prevenção

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E por último, um agradecimento à professora Ana Francisca Bettencourt, pela sua orientação e conselhos, que foram imprescindíveis nesta última etapa.

# Abbreviations and Acronyms

**BCoDE** Burden of Communicable Diseases in Europe

**CAUTI** Catheter-associated urinary tract infection

**CDC** Centers for Disease Control and Prevention

**CDI** Cardiac devices-related infections

**CNS** Coagulase-negative Staphylococcus

**CRBSI** Catheter-related bloodstream infection

**CRE** Carbapenem-resistant Enterobacteriaceae

**DALYs** Disability-Adjusted Life Years

**DAI** Device-associated Infection

**DGS** Direção-Geral da Saúde

**ECDC** European Centre for Disease Prevention and Control

**EEA** European Economic Area

**EPS** Extracellular polymeric substances

**ESBL** Extended spectrum beta-lactamase

**ET** Endotracheal tube

**HAI** Healthcare-associated infections

**HGT** Horizontal gene transfer

**ICD** Implantable Cardioverter Defibrillator

**IP** Intraperitoneal

**LPS** Lipopolysaccharide

**MIC** Minimum inhibitory concentration

**MRSA** Methicillin-resistant Staphylococcus aureus

**MSCRAMM** Microbial surface components recognizing adhesive matrix molecules

**NYHA** New York Heart Association

**PEG** Polyethylene glycol

**PD** Peritoneal dialysis

**PIA** Polysaccharide intercellular adhesin

**PNAG** Poly-N-acetylglucosamine

**PVE** Prosthetic valve endocarditis

**VAP** Ventilator-associated pneumonia

**WHO** World Health Organization

**YLLs** Years of Life Lost

**YLDs** Years Lost due to Disability

# Table of Contents

# List of Figures



# List of Tables

# 1. Introduction

The evolution in technology has greatly improved and revolutionized the practice of medicine. Medical devices are a part of this revolution and are still essential for the management of critically ill patients. Unfortunately, they are a major cause of hospital acquired infections (HAI), especially in intensive care units, and have forced health care providers, clinicians and hospital administrators to accept the necessity for nosocomial infections control.

However, there is hope in reducing HAI's, especially with the advances in technology regarding these devices. (1)

**Aim**

The aim of this revision is to describe the pathogenesis of device-associated nosocomial infections, to identify the management procedures and to pinpoint prevention strategies for these infections.

**Methods**

Published studies and reviews were identified with searches on PubMed, ResearchGate, ScienceDirect, Springer Link, Elsevier and Mendeley. The following keywords were used separately and combined in all databases and search engines: nosocomial infection, infection, hospital acquired infection, bacterial contamination, biofilm, healthcare equipment, catheter, endotracheal tube, prosthetic valves, peritoneal dialysis, pacemaker, cardioverter-defibrillators, management and prevention. Articles were considered eligible if they were published in peer-reviewed english-language journals in 2001 or later.

Information was also collected from published books, websites and reports from pertinent organizations like DGS (Direção-Geral da Saúde), CDC (Centers for Disease Control and Prevention) WHO (World Health Organization).

## 1.1 Nosocomial Infections

### 1.1.1 Definiton

An infection is a systemic or localized disease resulting from the presence of an infectious agent (s) or their toxins. (2)

A healthcare-associated infection (HAI), also known as nosocomial infection, is defined as an infection that is acquired by a patient during the process of care in a health care facility, and that was not present at the time of admission.

This also includes the infections that appear after discharge, and occupational infections among staff of the facility. (3)

The infectious agents that cause HAIs can have endogenous or exogenous sources. The endogenous sources are body sites normally colonized by local microbial flora, that under favourable circumstances can became invasive and/or cause infection. On the contrary, the exogenous sources are external to the patient, for example: patient care equipment, medical devices, the health-care environment, health-care workers and visitors. (4)

### 1.1.2 Epidemiology and Public Health Issues

HAI's are a significant public health-issue both for the health-care systems and the patient. They are the most common complication affecting hospitalized patients and are the fourth leading cause of disease in industrialised countries. (5)

In the European Point Prevalence Survey, the prevalence of patients with at least one HAI was 6% and the total annual number of patients that had at least one HAI in European hospitals in 2011-2012 was 3.2 million. (6)

It has been reported that annually an estimated 220,000 nosocomial Infections are acquired in health care-facilities in Canada. (7). Moreover, the results of a project known as the HAI Prevalence Survey, reported that in 2011, 4.0% of patients in U.S. acute care

hospitals had at least 1 health care–associated infection, there were an estimated 722,000 HAIs in these U.S. hospitals. (8)

On the other hand, according to the *Report on the Burden of Endemic Health Care-Associated Infection Worldwide*, in developing countries this can be an even bigger issue with the incidence of HAI ranging from 4.4% up to 88.9%. There are a number of aspects in these countries, that increase the risk of nosocomial infections: low financial resources, malnutrition, shortage of basic equipment, deficient hygiene and sanitation, insufficient or inadequate health infrastructures, lack of pharmacologic therapy, infections control practices and health-care workers. (4)

Of a total of 15.000 reported HAIs in the European PPS, the most frequently reported HAI types were respiratory tract infections (pneumonia 19.4 % and lower respiratory tract 4.1%), surgical site infections (19.6%), urinary tract infections (19.0%), bloodstream infections (10.7%) and gastro-intestinal infections (7.6%).

The presence of invasive devices in the days preceding the HAI onset was relevant for pneumonia, urinary tract infections and bloodstream infections. 33% of the pneumonia cases, 59.5% of urinary tract infections and 39.5 % of bloodstream infections were reported as device-associated. (6)

The number of deaths occurring in the European Union (EU) as a direct consequence of these infections is estimated to be at least 37.000 and it is thought that they contribute to an additional 110.000 deaths each year. (9) Reports from the US indicate that nosocomial infections accounts for 90,000 deaths per year (5) and in Canada more than 8.000 patients with HAI's die every year. (7)

In a study conducted by Cassini A. et al (10), the overall burden of HAI's was described in acute care hospitals of the EU and European Economic Area (EEA). Disability-Adjusted Life Years (DALYs) were calculated using the methodology of the Burden of Communicable Diseases in Europe (BCoDE) project and the results of the ECDC point prevalence survey of HAIs. Annually in the EU/EEA, 2.609.911 new cases of HAIs are accounted for a total of a 2.506.091 DALYs corresponding to 501 DALYs per

100.000 general population. Over 60% of the total DALYs were due to the acute phase of six HAIs, while the remaining were due to the sequelae. **Fig. 1.1 Estimated annual burden of six healthcare-associated infections in DALYs per 100.000 population split between YLLs and YLDs** summarizes the burden of these six types of HAI expressed in annual DALYs per 100.000 general population, distributed between Years of Life Lost (YLLs) and Years Lost due to Disability (YLDs).

Nosocomial Infections are also responsible for considerable economic costs. One of the greatest contributor to cost is the increased length of hospitalization for infected patients. Prolonged stay not only increases direct costs to patients or payers but also indirect costs due to lost days of work. The increase use of drugs, the need for isolation, and the use of additional laboratory and other diagnostic studies also contribute to costs. (3)

An estimated $9.8 billion is spent each year treating hospital-acquired infections in the US.

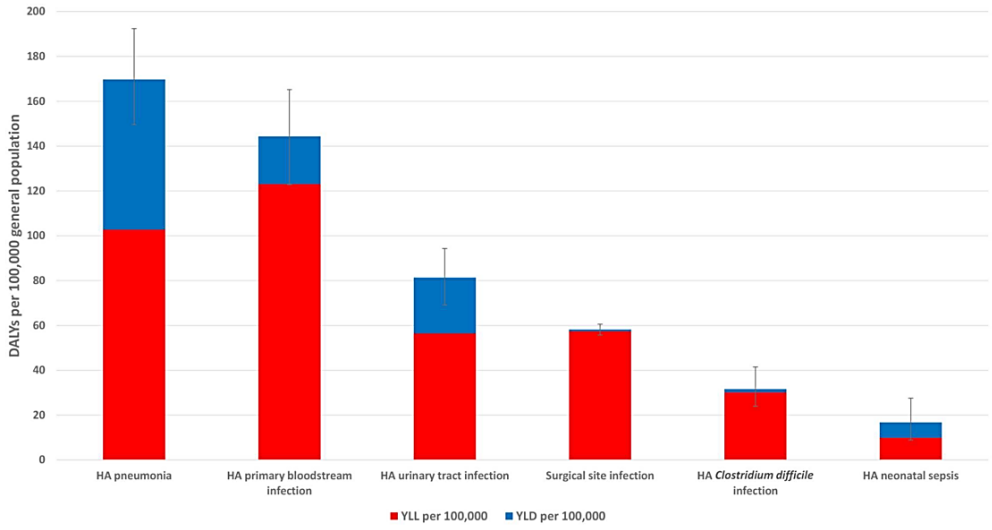


**Fig. 1.1 Estimated annual burden of six healthcare-associated infections in DALYs per 100.000 population split between YLLs and YLDs**
**Adapted from: (10)**

Of the 5 major HAIs, surgical site infections contributed the most to overall costs (33.7%), followed by ventilator-associated pneumonia (31.7%), central line–associated bloodstream infections (18.9%), Clostridium difficile infections (15.4%), and catheter-associated urinary tract infections (0,3%). (11)

In Europe, HAIs cause 16 million extra-days of hospital stay, and are accounted for approximately €7 billion per year in financial losses (considering direct costs only). (4)

## 1.2 Medical Devices

### 1.2.1 Concept

According to the EU Regulation 2017/745, a medical device is any instrument, apparatus, equipment, software or another item, used alone or in combination, (including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application) with the intention of being used on human beings with the purpose of:

a) diagnosis, prevention, monitoring, treatment or alleviation of disease;
b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
c) investigation, replacement or modification of the anatomy or of a physiological process;
d) control of conception;

A medical device does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means. (12)

There are different principles on which the classification rules of medical devices are based on.

The intended purpose is one of them, and it means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials

Another principle is the duration of contact with the patient, a medical device can be classified as transient when it is normally intended for continuous use for less than 60 minutes. Short term when it is normally intended for continuous use for not more than 30 days. And long term when it’s normally intended for continuous for more than 30 days.

It should be kept in mind that the duration of use should not be considered as the time taken to apply the product but rather the duration for which the product achieves its intended purpose.

One of the most complex principles for classification is invasiveness.

An invasive device is a device which, in whole or in part, penetrates inside the body through either a body orifice or the surface of the body. And a body orifice is defined as any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma.

In EU, the devices can be divided in classes: I, IIa, IIb and III. This classification must be processed in accordance with several rules. (13) Class III devices demand more supervision than the devices from other classes.

Most of implantable devices belong to this class, except for those that are destined to be placed in the teeth (IIa).

According to the EU Regulation 2017/745, an implantable device is any device, including those that are partially or wholly absorbed which is intended:

a) to be totally introduced into the human body, or
b) to replace an epithelial surface or surface of the eye, by clinical intervention and which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days is also designated an implantable device.

Since both class III and implantable devices are responsible for most of the problems resulting from medical device use, manufacturers should summarise the safety and performance aspects and the also the outcome of the clinical evaluation in a document publicly available. (12)

# 2. Nosocomial Device-associated Infections

The use of medical devices has increased dramatically over the previous decades. Today millions of patients worldwide benefit from devices ranging from permanent implants like pacemakers, replacement joints or stents, or from temporary inserted devices such as catheters. (14)

In the healthcare environment, these devices are used daily, and although they are supplied as sterile, the moment the packages are opened, handled and inserted into a patient they become exposed to microorganisms. (15)

Device-associated Infections (DAI) are always connected with microbial contamination. (14) The microorganisms responsible for the infections can either be the ones that colonize de human body or the ones colonizing the hospital environment itself. (15)

DAIs are the most preventable of nosocomial infections and are also classified has preventable medical errors. While non-device nosocomial infections often occur with patients with impaired host defence mechanisms and have no definable mode of spread, DAIs may involve healthier patients, frequently have well-defined mechanisms of pathogenesis and transmission and therefore have known methods of prevention. (16)

## 2.1 Pathogenesis: Adherence

The same properties that make a medical device biocompatible for human cells also provide a welcoming environment for bacteria. Anthony Gristina (17) coined the phrase “race for the surface” which illustrates the events that take place upon insertion of the device: host cells and bacteria compete for space in the device’s surface.

One hopes that the race is won by the host tissue, “defending” the surface from invading pathogens, because device microbial colonization is in many cases the prelude to a medical device associated infection. (18)

Adhesion takes place due to initial attraction of the bacterial cells to the device's surface. Bacteria moves to the material surface due to physical forces and chemical factors that include: Brownian movement, Van der Waals attraction, gravitational forces, surface electrostatic charges and hydrophobic interactions. (19)

This process also results from the multifaceted interaction between bacterial, environment, device and host factors. (20)

## 2.1.1 Bacterial Factors

***Staphylococcus epidermidis* and *Staphylococcus aureus***

The adherence process of *S. epidermidis* and *S. aureus* to the surface is not a one-time phenomenon.

Initially the attachment of *S. epidermidis* is mainly governed by bacterial cell surface hydrophobicity. Specific proteins such as the surface protein AtIE, a bifunctional adhesin/autolysin, and the Bap/Bhp protein contribute to this hydrophobic character.

On the other hand, *S. aureus* appears to be more dependent on the presence of host-tissue ligands. Fibronectin and fibrinogen binding proteins are the major adhesins involved in the adherence of the *S. aureus* to the medical device's surface. They are part of a family of surface proteins referred to as "Microbial surface components recognizing adhesive matrix molecules" or MSCRAMM.(20)

The most important MSCRAMMs include FnbpA and FnbpB (fibronectin binding proteins), ClfA (clumping factor), ebpS (elastin binding protein) and cna (collagen adhesin). (21)

In staphylococci this initial phase is followed by an intercellular aggregation that is mediated by a poly-N-acetylglucosamine (PNAG) homopolymer, encoded by the ica operon, named PIA (polysaccharide intercellular adhesin) that surrounds and connects staphylococci cells in a biofilm. (21)

### *Escherichia coli* and *Pseudomonas Aeruginosa*

The successful adhesion of these two Gram-negative bacteria to surfaces is dependent on the presence of functional flagella that enables the bacteria to swim and overcome repulsive electrostatic forces that may exist between the cell surface and the surface of material. (22)

Type 1 fimbriae, curli and conjugative pili are three classes of cell appendages that have a role in strengthening the interactions between *E. coli* and the surface, and promote irreversible attachment.

The expression of type 1 fimbriae is induced by adhesion and some findings suggest that the type 1 fimbrial FimH adhesin, besides binding eukaryotic mannose oligosaccharides, also have nonspecific binding activity at abiotic surfaces. (23)

Curli fimbriae, which are extracellular structures that attach to the proteins of the extracellular matrix, and conjugative pili, which are known to allow bacterial conjugation, promote cell to surface interaction and cell-to-cell communication. (24)

In *P. aeruginosa*, type IV pili and lipopolysaccharide A and B aid initial surface adhesion. It has been discovered that the bacteria could alter its phenotypic lipopolysaccharide composition to enhance adherence: the production of lipopolysaccharide-A increased the hydrophobicity of the cell surface and increased adhesion to hydrophobic surfaces and the opposite was true of lipopolysaccharide-B with increased hydrophilicity and adhesion to hydrophilic surfaces.

Intercellular adhesion is increased by the production of lectins, such as PA-IL and PA-IIL (also known as LecA and LecB). (22)

### *Klebsiella pneumoniae*

The attachment to abiotic surfaces of *K. pneumoniae* is mediated by type 1 and type 3 fimbriae. (25)

Type 3 fimbriae have been demonstrated to be the major appendages that mediate the formation of biofilms on biotic and abiotic surfaces, growth of *K. pneumoniae* on abiotic surfaces is particularly facilitated by the MrkA type 3 fimbrial protein.

It has also been proven that LPS (lipopolysaccharide) is involved in the initial adhesion on abiotic surfaces and that the capsule is necessary for proper initial bacterial coverage of the substratum. (26)

***Candida albicans***

Eap1 (Enhanced Adherence to Polystyrene 1) is a known important adhesin for the binding of *C. albicans* to the surface.

The closely related cell wall proteins Als1 and Als3 (Agglutinin like Sequence) promote binding to several protein-coated substrates which may resemble the surface of an inserted medical device. (27) Additionally, adhesins from this ALS gene family are responsible for cell-to-cell adherence.

Hwp1 (Hyphal Wall Protein 1) is also involved in intercellular aggregation, and it seems likely that Hwp1 and Als1/Als3 interact on cell surfaces and mediate cell-binding. Rbt1 (Repressed by TUP1) which is in the same adhesin family as Hwp1, promotes surface hydrophobicity, mediates adherence to polystyrene and has high aggregation potential. (28)

Although, these proteins are expressed at much higher levels in hyphal cells than in yeast cells, it is possible that the initial adherence step that leads to biofilm formation *in vivo* can be carried out by either yeast-form cells or hyphae. (27)

A recap of the different microorganism's adhesion factors can be found in **Table 2.1**.

**Table 2.1 Summary of microorganism's adhesion factors**

| Microorganisms | Adhesion Factors | References |
|---|---|---|
| ***S. epidermidis*** | **Surface adhesion (Hydrophobic character):**<br>- Surface protein AtlE;<br>- Bap/Bhp protein; | (16)<br>(18) |
| | **Intercellular aggregation:**<br>- PIA (polysaccharide intercellular adhesin); | |
| ***S. aureus*** | **Surface adhesion (MSCRAMMs):**<br>- FnbpA and FnbpB which binds to fibronectin;<br>- ClfA (clumping factor), which binds to fibrinogen;<br>- ebpS which binds to elastin;<br>- cna which binds to collagen; | (17)<br>(18) |
| | **Intercellular aggregation:**<br>- PIA (polysaccharide intercellular adhesin); | |
| ***E. coli*** | **Movement:**<br>- Flagella; | (19)<br>(20) |
| | **Surface adhesion and intercellular aggregation:**<br>- Type 1 fimbriae;<br>- Curli pili;<br>- Conjugative pili; | |
| ***P. aeruginosa*** | **Movement:**<br>- Flagella; | (19)<br>(21) |
| | **Surface adhesion:**<br>- Type IV pili;<br>- Lipopolysaccharide A and B; | |
| | **Intercellular aggregation:**<br>- PA-IL;<br>- PA-IIL; | |
| ***K. pneumoniae*** | **Surface adhesion and intercellular aggregation:**<br>- Type 1 fimbriae;<br>- Type 3 fimbriae;<br>- LPS;<br>- Capsule; | (22)<br>(23) |
| ***Candida albicans*** | **Surface adhesion and intercellular aggregation:**<br>- Eap1;<br>- Als1 and Als3;<br>- Hwp1;<br>- Rbt1; | (24)<br>(25) |

## 2.1.2 Environmental and Device Factors

Certain factors in the general environment (**Table 2.2**) and several device-related factors ( **Table 2.*3***) can affect bacterial adherence to the medical device.

Flow conditions are a well study environmental factor that impacts bacterial adherence. The interactions between moving water and microbial biofilm can lead to viscoelastic deformation, rolling, ripping and material detachment, consequently this influences the number or attached bacteria. Turbulent flows result in higher detachment forces, removing more bacterial cells than laminar flow. (31)

Ionic strength and pH are responsible for changes in the surface characteristics of both the bacteria and the material: hydrophobicity and charge. The surface charge greatly influences the adhesion force by controlling the electrostatic interaction, and the bacterial adhesion forces are enhanced by increasing surface hydrophobicity. (32)

Temperature leads to changes in both bacterial physiology and chemical or physical adsorption of adhesive polymers. (33)

And the presence of antibiotics in the environment also influences adhesion, it decreases bacterial adhesion depending on bacterial susceptibility and antibiotic concentration. (20)

**Table 2.2 Environmental factors that influence bacterial adherence**

| Environmental Factors | | References |
|---|---|---|
| **Flow conditions** | - Influences the number of attached bacteria;<br>- Turbulent flows result in higher detachment forces, removing significantly more bacterial cells than laminar flow; | (31) |
| **Ionic strength and pH** | - Changes surface characteristics of both the bacteria and the materials: hydrophobicity and charge;<br>- Surface charge greatly influences the adhesion force by controlling the electrostatic interaction;<br>- Surface hydrophobicity enhances bacterial adhesion forces; | (32) |
| **Temperature** | - Influences bacterial physiology;<br>- Influences chemical or physical adsorption of adhesive polymers; | (33) |
| **Presence of antibiotics** | - Decreases bacterial adhesion depending on bacterial susceptibility and antibiotic concentration; | (20) |

Device-related factors are modifiable and important in the prevention of the possible infection that can arise from bacterial adhesion and biofilm formation.

Some materials favour bacterial adherence more than others. Their source also has an impact, for example synthetic materials facilitate adhesion more than natural materials. Shape of the medical device can also influence this process. And irregular, textured or hydrophobic surfaces are more prone to suffer bacterial attachment than regular, smooth or hydrophilic ones. (20)

**Table 2.3 Device-related factors that favour bacterial adherence**

| **Device-Related Factors** | |
|---|---|
| **Type of device (material)** | - Polyvinyl chloride favours bacterial adherence more than does Teflon;<br>- Polyethylene favours bacterial adherence more than does Polyurethane;<br>- Latex favours bacterial adherence more than does Silicone<br>- Silicone favours bacterial adherence more than does Polytetrafluoroethylene;<br>- Stainless steel favours bacterial adherence more than does Titanium; |
| **Source of device material** | - Synthetic favours bacterial adherence more than does biomaterial; |
| **Surface** | - Irregular favours bacterial adherence more than does regular;<br>- Texture favours bacterial adherence more than does smooth;<br>- Hydrophobic favours bacterial adherence more than does hydrophilic; |
| **Shape** | - Polymeric tubing favours bacterial adherence more than does wire mesh; |

Adapted from (20)

## 2.1.3 Host Factors

Host factors can be divided into 2 groups:

(1) Host factors that affect bacteria adherence to the device, these include serum or tissue proteins like albumin, fibronectin, fibrinogen, thrombin and denaturized collagen.

(2) Host factors that can either promote or inhibit the persistence of already adherent bacteria on the surface of the device. (20)

Examples of these two types of host factors can be found in **Table 2.4**

**Table 2.4 Host Factors that influence bacterial adhesion**

| Host Factors | | References |
|---|---|---|
| **Albumin** | - When adsorbed on the material surface, prevents binding of microorganisms; | (19) |
| **Fibrinogen** | - When adsorbed on the material surface, favours the adherence of bacteria; | |
| **Fibronectin** | - Promotes adhesion, by binding in ligand-receptor type of interaction with bacterial proteins; | |
| **Thrombin** | - Polymerises fibrinogen to fibrin, which stabilizes the thrombus, leading to an increase in bacterial adhesion; | |
| **PMNs** | - Those that have been in contact with the medical device have lower bactericidal activity, which promotes bacterial persistence; | (34) |
| **IFN-γ** | - Induces major histocompatibility complex class II proteins on phagocytic cells, activating mononuclear phagocytes, and regulating humoral immune responses, inhibiting bacterial persistence; | (20) |

## 2.2 Pathogenesis: Biofilms

Biofilms have been defined as a naturally occurring aggregates of microorganisms of a single or multiple species, in a self-produced extracellular polymeric matrix, that is adherent to either a biologic or non-biologic surface.

Biofilm communities differ profoundly from the free-living bacteria cells. They are complex systems with a high cell density ($10^8$ to $10^{11}$ cells $g^{-1}$ wet weight) that have emergent properties (**Fig. 2.1**) (35)

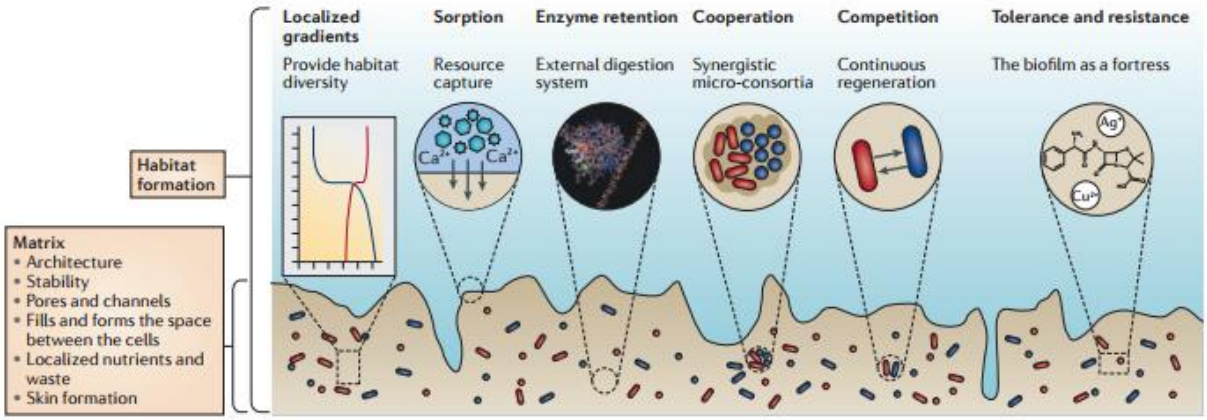


**Fig. 2.1 Emergent Properties of Biofilms and Habitat formation**
**Adapted from: (35)**

As we have seen before, the first step in biofilm formation is the adherence or attachment of planktonic (free floating) bacteria to the surface. As bacteria start to multiply, attachment strengthens and becomes irreversible. Adherent cells up-regulate the secretion of inter-cellular signalling molecules that are responsible for a community-wide phenotypic response through a process named “quorum sensing”. Further maturation takes place, with the consumption of soluble nutrients, excretion of extracellular polymeric substances (EPS), up regulation of virulence factors and recruitment of other bacterial species or mammalian cells.

The next step is the formation of microcolonies with multi-layered cells and then the development of matrix-enclosed “towers” or “mushrooms” of microbial cells.

In the final stage the biofilm reaches a critical mass and disperses planktonic bacteria ready to colonize other surfaces. (**Fig. 2.2**) (36)

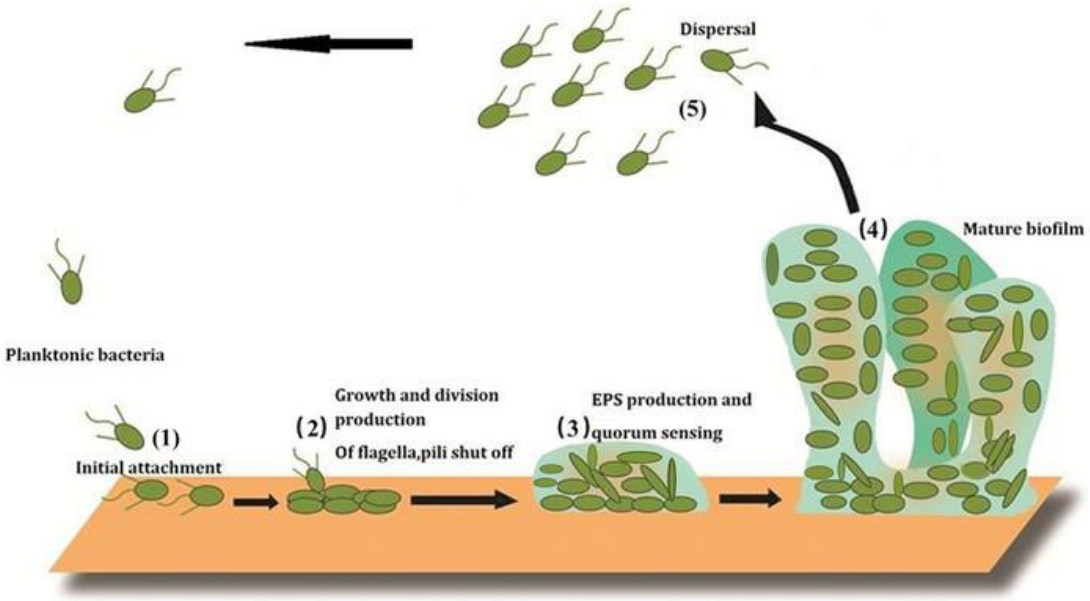


**Fig. 2.2 Biofilm formation.**
**Adapted from: (91)**

## 2.2.1 Quorum sensing

Bacteria that form a biofilm can regulate their cooperative activities and physiologic processes by producing, detecting and responding to small diffusible signal molecules called autoinducers. This process is called quorum sensing.

Quorum sensing systems have been divided into at least three classes:

(1) LuxI/LuxR-type, in Gram-negative bacteria, which use acyl-homoserine lactones (AHL) as signal molecules;

(2) Oligopeptide-two-component-type, in Gram-positive bacteria, which use small peptides as signal molecules;

(3) LuxS-encoded autoinducer 2 (AI-2) type, in both Gram-negative and Gram-positive bacteria.

Each type of signal molecule is detected and responded by a precise sensing apparatus and regulatory network. (37) The AHLs and oligopeptides are designed for intra-species

signalling, however the AI-2 allows interspecies communication, and cross-species social interaction. (36)

During quorum sensing, bacterial cells cooperate to obtain group-specific benefits.

There is a phenomenon controlled by this mechanism called altruism, in which cooperation benefits the group but the cooperating individual is sacrificed. (37)

Since natural selection is blind to which individual cells pass on a given set of genes, as long as those genes are replicated and the information preserved, sometimes a cell's best strategy may be to sacrifice itself while benefiting other cells that are genetically identical. (38)

Virulence factors production and secretion, which are important in the pathogenesis of the infection, is also regulated by quorum sensing. (37)

## 2.2.2 Genetic exchange

Biofilms also provide an ideal environment for genetic exchange. Horizontal gene transfer (HGT) in bacteria can be conducted through three different mechanisms: direct cell–cell contact (conjugation), bacteriophage-mediated DNA transfer (transduction) and uptake of naked DNA by competent cells (transformation) (**Fig. 2.3**).

In conjugation, plasmids and conjugative transposons can be spread from a bacterial cell to members of its own and other species, between Gram-negative and Gram-positive bacteria, and even from bacteria to yeast, plants and mammalian cells.

Transduction describes HGT mediated by bacteriophages. When new phage particles are produced, DNA originating from the phage-infected bacterial cell may be packed into the phage particles and transferred to new bacterial hosts.

Transformation is the uptake of free DNA from the surrounding environment. Most often, cells reach an inducible, competent state that enables the DNA uptake.

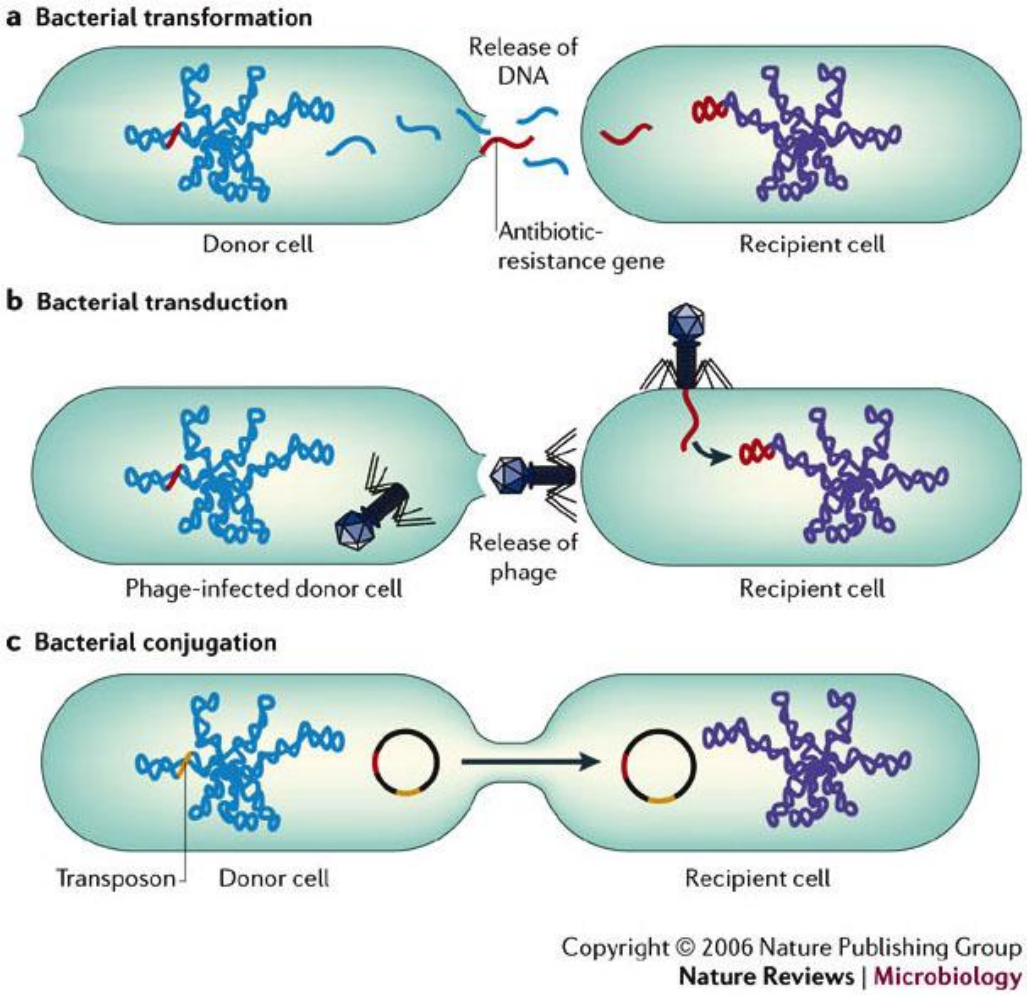


**Fig. 2.3 Horizontal Gene Transfer Mechanisms.**
**Adapted from: (92)**

Conjugation occurs in higher frequencies between members of biofilm communities than when in a planktonic state. The explanation for this is that biofilms are dense communities that facilitate the spread of mobile genetic elements (MGEs).

Besides conjugation, transformation is also known to occur at higher rates in biofilms, this process not only involves small DNA fragments but also big elements such as plasmids. (39)

Since plasmids may encode for resistance to multiple antimicrobial agents the HGT provides a mechanism for selecting for, and promoting the spread of, bacterial resistance to antimicrobial agents among other characteristics. (40)

## 2.2.3 Phenotypic differentiation

Phenotypic differentiation produces functionally specialize cells, with the purpose to help individual cells in a biofilm resist environmental conditions. These cells have target purposes within the community, including the expression of different receptor-ligands for surface adhesion, production of extracellular matrix polymers, metabolic regulation, and maintenance of the integrity or dissolution of the architecture of the biofilm. (36)

An important example of the differentiation is the “persister” phenotype, which has a role in bacterial antibiotic resistance. These cells are in dormant state, as many antibiotics affect growing cells, dormant cells can resist short treatments and afterwards revert to active growth to restore the population. (37)

Phenotypic differentiation contributes for the overall development of the biofilm by producing and maintaining biodiversity and ecosystem microbial homeostasis. (36)

## 2.3 Related to Common Medical Devices

### 2.3.1 Urinary Catheter

Immediately after urinary catheter insertion microorganism adhere to a film of host proteins, that is formed along the catheter surface, and biofilm formation can begin. Urine components like Tamm-Horsfall protein and magnesium and calcium ions are incorporated into the extra-cellular mucopolysaccharide of the biofilm. (41)

Most of the microorganism causing catheter-associated urinary tract infections (CAUTI) are from the endogenous microbiota, typically via meatal, rectal or vaginal colonization, they ascend the urethra to reach the bladder. A smaller proportion of the microorganisms are from exogenous sources, such as via contaminated hands of healthcare personnel or equipment.

Pathogens can enter the urinary tract by two routes. In the extraluminal route the migration occurs along the outside of the catheter in the periurethral mucous sheath, and in the intraluminal route, the movement occurs along the internal lumen of the catheter from a contaminated collection bag or catheter-drainage tube junction. (42)

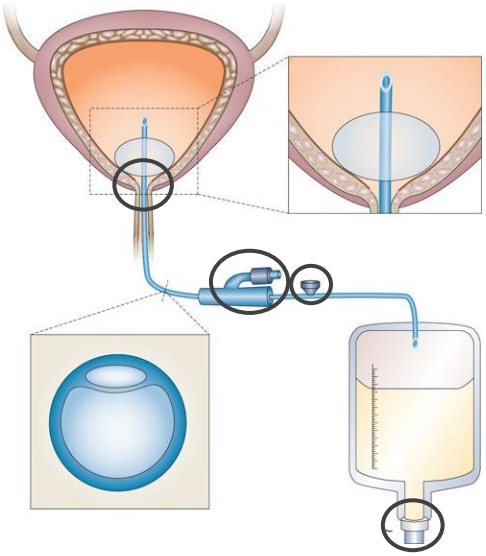

**Fig. 2.4 Entry points for bacteria causing catheter-associated urinary tract infections.**
**Adapted from: (45)**

After insertion of a short-term catheter, the initial infection is usually with a single organism, E. coli or other Enterobacteriaceae are the most common. Yeast species like Candida spp., Enterococcus spp., coagulase negative Staphylococcus and Pseudomonas aeruginosa may also occur.

When there is a chronic indwelling catheter, on average three to five organisms can be isolated from the urine. (43) Proteus mirabilis is an organism of unique importance for these patients, the longer a catheter is placed the more likely P. mirabilis will be present. This organism produces more copious biofilm than other bacteria, and tend to persist for longer periods of time. (41) Klebsiella pneumoniae, Morganella morganni and P. stuartii are also common.

The urine of patients with indwelling catheters in both acute and long term care facilities, is a major site of isolation of antimicrobial-resistant organism, such as Extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae and Carbapenem-resistant Enterobacteriaceae (CRE). (41)

Although bacterial factors are crucial for the pathophysiology of CAUTI's, there are also some key host factors. **Table 2.5** outlines these major risk factors, both the modifiable and the nonmodifiable ones. They must be taken in consideration in the design and implementation of interventions for the prevention of these infections.

Due to heavy bacterial colonization of the perineum, females have a higher risk of developing CAUTI. Other factors identified include rapidly fatal underlying illness; age greater than 50 years, nonsurgical disease, catheter insertion after the sixth day of hospitalization, catheter inserted outside the operating room, diabetes mellitus and serum creatinine greater than 2 mg/dL at the time of catheterization. Nonadherence to aseptic catheter care recommendations has also been associated with increased risk of infection. (44)

**Table 2.5 Risk factors for CAUTI**

| Non-modifiable Factors | Modifiable Factors |
|---|---|
| Female sex | Duration of catheterization |
| Severe underlying illness | Non-adherence to aseptic catheter care |
| Nonsurgical disease | Lower professional training of inserter |
| Age > 50 | Catheter insertion outside operating room |
| Diabetes | Catheter insertion after sixth day of hospitalization |
| Serum creatinine >2 mg/dL | |

Adapted from (45)

## 2.3.2 Intravascular Catheter

Much like urinary catheters, upon insertion of intravascular catheters into the bloodstream, the surface is rapidly coated with host-derived matrix proteins (fibrin, fibrinogen, fibronectin, collagen, elastin and laminin). Over the next 24 h a fibrin sheath forms and attracts platelets and coagulation factors, and promotes leukocyte adherence as it continues to evolve over time. The fibrin sheath (**Fig. 2.5**) is one of the most common causes of thrombotic occlusion.

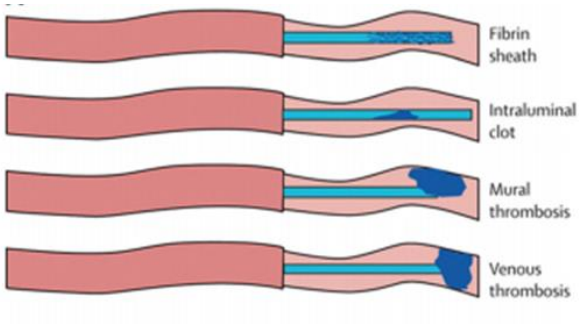


**Fig. 2.5 Evolution of the fibrin sheath.**
**Adapted from: (45)**

Microorganisms can bind to both the adsorbed proteins at the surface of the catheter, and the proteins within the thrombus, such as fibrinogen and fibronectin. They then start colonizing the medical device and forming a biofilm, as early as 24h after the catheter placement. (45)

The catheter can be contaminated by four recognized routes (**Fig. 2.6**):

1) Migration of skin organisms at the insertion site into the cutaneous catheter tract and along the surface of the catheter with colonization of the catheter tip; this is the most common route of infection for short-term catheters;
2) Direct contamination of the catheter or catheter hub by contact with hands or contaminated fluids or devices;
3) Less commonly, catheters might become hematogenously seeded from another focus of infection;
4) Rarely, infusate contamination might lead to infection (29)

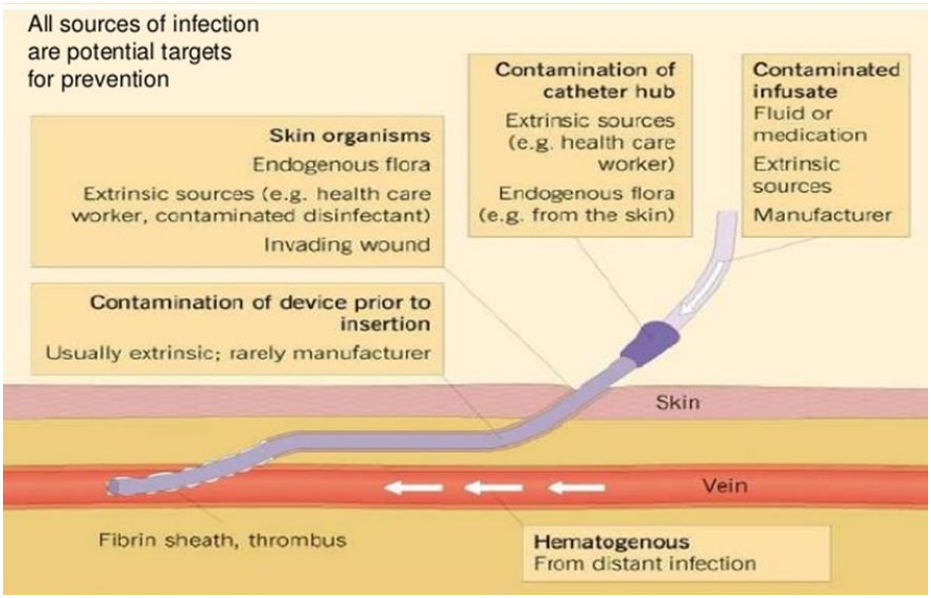


**Fig. 2.6 Vascular Catheters Potential Routes of Contamination. Adapted from: (47)**

According to Ramanathan Parameswaran et al. (46), 64% of the pathogens causing catheter-related bloodstream infection (CRBSI) were Gram-positive, and 36% were Gram-negative. The most common pathogens were S. aureus 40%, P. aeruginosa 16%, Coagulase negative staphylococci 8%, E. coli 8%, K. pneumoniae 8%, and Acinetobacter baumanii 4%. (47)

There are several risk factors for CRBSI onset (**Table 2.6**). It has been shown that CRBSI is more likely to occur with prolonged catheterization. Patients with advanced age and multiple underlying diseases and diabetes usually show decreased immune function. In addition, parenteral nutrition provides an excellent environment for bacterial growth and reproduction. Even though these host factors are important, the strategies of prevention and management of infection are design according to catheter factors, because these are the modifiable ones. (48)

**Table 2.6 Risk factors for CRBSI**

| Non-modifiable Factors | Modifiable Factors | References |
|---|---|---|
| Chronic Illness | Duration of catheterization | (48) (29) |
| Bone marrow transplantation | Type of catheter | |
| Immune deficiency | Conditions of insertion | |
| Previous history of CRBSI | Skill of the person who inserted the catheter | |
| Old age | Density of skin flora at the catheter insertion site | |
| Diabetes | | |

## 2.2.3 Endotracheal tube

The introduction of an endotracheal tube (ET) in the airways has several consequences that favour the development of a biofilm on the distal part of the ET:

(1) Impairment of natural host-defence mechanisms including the cough reflex;

(2) Pressure on the tracheal wall, decreasing the mucosal integrity and mucociliary clearance, resulting in the accumulation of tracheobronchial secretions (i.e. mucus);

(3) Transfer of bacteria from the highly-colonized oropharynx to the sterile tracheobronchial this happens because even though the cuff of the ET act as a seal between the sterile lungs and the upper colonized airways, the presence of folds along the inflated cuff impairs sealing. (49)

Colonization and biofilm development on the ET happens within 24 hours of intubation. When a biofilm is formed on an ET, aggregates of cells might be dispersed and be moved to the lower respiratory tract during the process of positive pressure ventilation. This plays an important part in the development of ventilator-associated pneumonia (VAP). VAP is likely to occur to 9-27% of intubated patients and it is one of the most common acquired infections in the ICU. (50)

It has been reported that 80% of all VAP episodes are correlated with the ESKAPE pathogens (i.e. Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.). (49)

Both S. aureus and P. aeruginosa are responsible for the majority of VAP cases. Since S. aureus is a part of human nasal flora, it's easy to understand why it is one of the most common and important causes of VAP. P. aeruginosa is the most antibiotic-resistant pathogen causing VAP and the deadliest, causing the most fatal episodes.

Bacteria from the Enterobacteriaceae family, such as E. coli, K. pneumoniae and Enterococcus, are a serious threat for patients that are immunocompromised, have a

critical illness or are doing antibiotic therapy. Since these conditions can supress the normal bacterial flora, they cause an overgrowth of Enterobacteriaceae lower gastrointestinal tract and lead to colonization in the respiratory tract. (51)

Acinetobacter spp. is not frequently found in healthy humans, but it can cause severe infections in critically ill intensive unit patients, it is an important cause of outbreaks and spreads easily and quickly from one patient to another.

It's also not surprising that the typical oral bacteria are present in ET biofilms, because these biofilms are inoculated by oral secretions. Although members of the oral floral are commensal bacteria (Bacteroidetes, Actinobacteria, Clostridia, Fusobacteria and Proteobacteria) and are mostly harmless, a model of biofilm formation suggests that they play a role on the early stages of biofilm formation and interact with nosocomial pathogens (**Fig. 2.7**)

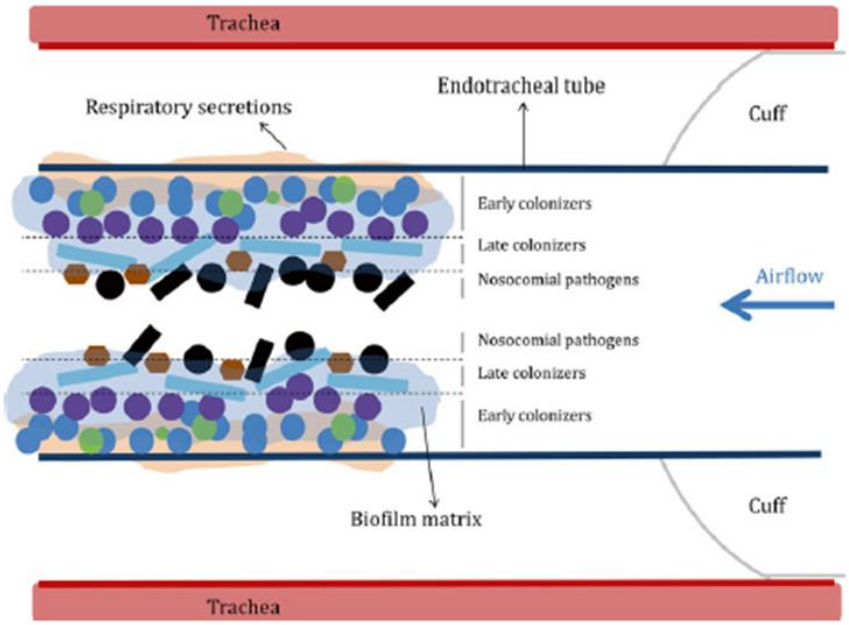


**Fig. 2.7 Model of biofilm formation on the distal end of the ET**
**Adapted from: (49)**

When leakage occurs at the cuff of the ET, nasopharyngeal secretions (containing oral bacteria) accumulate at the distal end of the ET. Examples of the early colonizers are Streptococcus oralis, Streptococcus mitis and Streptococcus sanguis. These

streptococci aggregate with a variety of oral bacteria enabling them to start colonization and initiating the formation of biofilms, exploiting saliva as a nutrient source.
Then other bacteria are attracted by the primary colonizers. One example is Veillonella spp., these bacteria are responsible for attracting Fusobacterium nucleatum., which acts as a switch between early and late colonizers (i.e.: Prevotella spp.).
In the end, nosocomial pathogens adhere onto the biofilm formed by the oral bacteria.

Although oral bacteria can initiate biofilm formation on the ET it must be noted that they are not directly involved in the onset of VAP. They simple provide a suitable environment that facilitates the adherence of potential respiratory pathogens. (49)

Besides bacterial factors there are several other risk factors that favour the onset of VAP (**Table 2.7**). Factors that enhance colonization of the oropharynx and/or stomach by microorganisms, like administration of antimicrobial agents or the presence of underlying chronic lung disease and conditions that favour aspiration in respiratory tract or reflux from G.I tract like repeat endotracheal intubation, supine position and coma, should be taken in consideration. (52)

Improper hand washing and failure to change gloves between contacts with patients results in the cross-contamination of patients and are the most important personnel-related and modifiable risk factors. (53)

Both the repeated insertion of an ET soon after its removal from a patient who is taken off ventilatory support and the long duration of intubation are risk factors for pneumonia.

It has also been observed that changing the ventilator circuit every 48 hours rather than 24 hours did not result in increase in contamination, in fact ventilatory circuit changes every 24 hours was shown to be a risk factor for VAP. (52)

**Table 2.7 Risk factors for VAP**

| Non-Modifiable Factors | Modifiable Factors | References |
|---|---|---|
| Underlying chronical lung disease (CPOD and ARDS) | Duration of intubation | (52) (53) |
| Aspiration of gastric contents | Patients' body position | |
| Number of intubations | Repeat insertion of the endotracheal tube soon after it is removed | |
| Medication (Antibiotics and Steroids) | Improper hand washing | |
| Immunosuppression | Failure to change gloves between contacts with patients | |
| Level of consciousness | Ventilatory circuit changes every 24 hours (rather than every 48 hours) | |

## 2.4 Related to Specialized Medical Devices

### 2.4.1 Peritoneal Dialysis

Peritoneal dialysis (PD) is a home-based dialysis treatment that it an effective alternative to hemodialysis. (54) PD is used in patients with end-stage kidney disease in more than 200,000 patients across 130 countries worldwide and accounts for 11% of the global dialysis population. (55)

In this treatment, a catheter is inserted permanently into the peritoneal cavity, where the dialysate solution is introduced and subsequently drained. The peritoneum acts as a filter allowing excess water and waste products from the blood to pass into the dialysate solution and be removed from the body.

The PD catheter, although it is considered a lifeline for these patients, also serves as a locus for infection. PD catheter-related infection is an important cause of morbidity, technique failure, and mortality. (54)

PD catheter related infections are represented by exit-site infections (ESI), tunnel infections (IS) and peritonitis.

ESI and TI per se pose little risks but the possibility of developing PD peritonitis demands careful attendance to these problems, it is estimated that 12% of these cases result in PD peritonitis. The infection may be caused by the surgical procedure to insert a PD catheter or the conduct of PD. (56)

The peritoneum can be contaminated from several sources, the most common being transluminal route, where there is touch contaminations of the spike, discontinuities of tubing or dialysis fluid contamination and pericatheter route, where occurs migration of organism from the skin along to the catheter into the peritoneum.

Transvisceral, transvaginal, hematogenous routes, and contamination of the water used to manufacture dialysate are less common, but also important. (57)

Gram-positive bacteria, specifically staphylococci and streptococci, are more common associated with PD peritonitis whereas gram-negative organisms are less common.

S. epidermidis are responsible for 26.5% of the cases followed by Streptococcus spp. 12.6%, S. aureus 9.8%, coagulase-negative staphylococci other than S. epidermidis 8.0%, Enterococcus spp. 5.9%, Klebsiella spp. 5.9%, E. coli 4.4%, other Enterobacteriaceae spp. 4.4%, Acinetobacter spp. 3.0%, Pseudomonas spp. 2.3%, and fungi 4.2%.

S. aureus is associated with more treatment failures than other gram-positive organisms, and gram-negative peritonitis has worse clinical outcomes than gram-positive infections. Fungal infection is associated with high rates of treatment failure, patient morbidity, and mortality. (58)

Reported risk factors for PD peritonitis are listed in **Table 2.8**. Most these are factors that increase the risk of infection like diabetes mellitus, frailty and comorbid disease burden, or increase the risk of peritonitis specifically such as positive nasal S. aureus carrier status, and previous history of exit-site infection. There are also a lot of demographic factors that have been associated with the increased risk, for example: age, sex and ethnicity. (55)

**Table 2.8 Risk factors for PD Peritonitis**

| Non-Modifiable Factors | Modifiable Factors | References |
|---|---|---|
| Older age | Obesity | (55)<br>(54) |
| Female sex | Smoking | |
| Indigenous racial origin | Hypoalbuminemia | |
| Black ethnicity | Hypokalemia | |
| Diabetes | Nasal Staphylococcus aureus carrier status | |
| Coronary artery disease | Biocompatible fluids | |
| Chronic lung disease | Previous exit-site infection | |
| Hypertension | Prior hemodialysis | |
| Poor residual kidney | Uraemia | |

## 2.4.2 Pacemakers and Cardioverter-Defibrillators

In the 11th World Survey of Cardiac Pacing and Implantable Cardioverter-Defibrillators, undertaken in 2009, it was observed that more than 1 million pacemakers and more than 300.000 cardioverter-defibrillators (ICD) were implanted that year. (59) Since then, rates of implantation increased and unfortunately this trend has been accompanied by an increase in the number of infections related to cardiac devices (CDIs). (60)

Pacemakers and ICDs are composed by 2 main components (**Fig. 2.8**). The generator which is a small electronic device that produces an electrical signal to stimulate atrial and ventricular activity, and the wire leads that have an electrode tip that is implanted into the heart muscle. The generator is implanted under the skin (typically on the chest wall), and delivers pulses down the leads that go through the large veins into the right heart, terminating in the right atrium, right ventricle, or both. ICDs also have the capability to recognize and shock ventricular arrhythmias. (61)

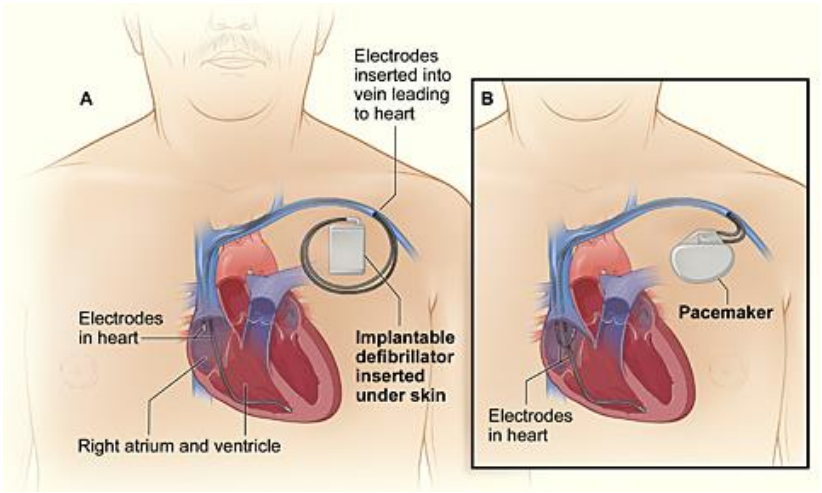


**Fig. 2.8 Comparison of an Implantable Cardioverter Defibrillator and a Pacemaker.**
**Adapted from: (93)**

In CDIs, there are two main routes of contamination. The pocket can become contaminated at the time of implantation during the surgical manipulation of the pocket, or if the generator or subcutaneous electrodes erode through the skin. Pocket infection may track along the intravascular portion of the electrode to involve the intracardiac portion of the pacemaker or ICD.

On the other hand, the pocket or the intracardiac portion of the electrode may become infected through hematogenous seeding during bacteremia or fungemia from a different source.

The microorganism responsible for the infections may be acquired endogenously from the skin of patients or exogenously from the hospital environment or workers. (62) The most frequent pathogens include common skin flora microorganisms like Coagulase-negative staphylococcal species and S. aureus.

Enterococcus and streptococcus accounts for 3% to 9% of isolated organisms in CDIs and gram-negative bacteria also represents for 3% to 9% of the pathogens responsible for these infections. (61)

There are several factors that increase the risk of CDI (**Table 2.9**). Studies suggest that people with diabetes mellitus, renal dysfunction and heart failure are more likely to have an infection. And it has also been identified that oral anticoagulant and long-term corticosteroid use can instigate the infection. (62)

Patient advance age, female sex and the inexperience of the operator are also some of the risk factors associated. (63)

**Table 2.9 Risk Factors for CDI**

| Non-Modifiable Factors | Modifiable Factors | References |
|---|---|---|
| Advance age | Type of device | (61)<br>(62)<br>(63) |
| Female sex | Operator inexperience | |
| Diabetes mellitus | Device revision/replacement | |
| Renal dysfunction | Amount of indwelling hardware | |
| Heart failure | Periprocedural factors, including the failure to administer perioperative antimicrobial prophylaxis | |
| Previous treatment with oral anticoagulant and corticosteroid | | |

## 2.4.3 Prosthetic Heart Valves

After years of improvements in the design and materials used for prosthetic heart valves, valve replacement surgery has improved dramatically and is now performed with low morbidity and mortality. (64) About 280 000 valve substitutes are implanted worldwide each year, approximately half are mechanical valves and half are bioprosthetic valves.

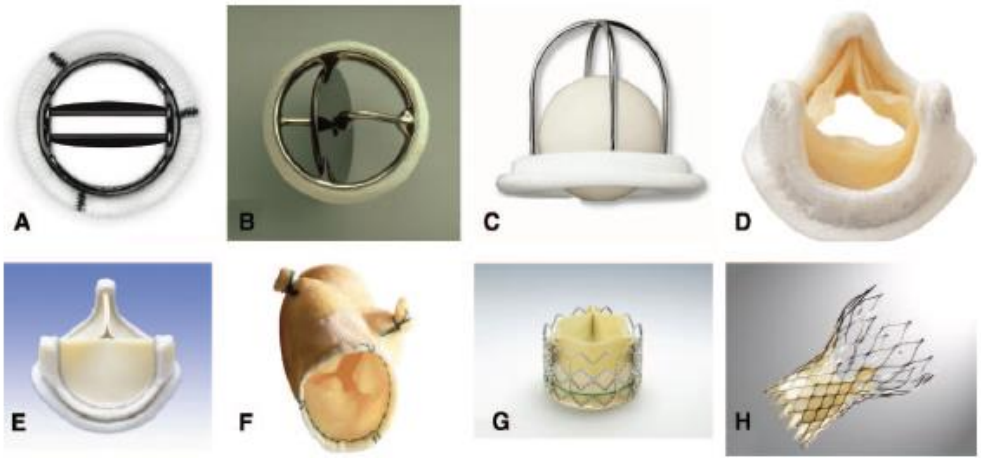


**Fig. 2.9 Different types of prosthetic valves. A, Bileaflet mechanical valve (St Jude); B, monoleaflet mechanical valve (Medtronic Hall); C, caged ball valve (Starr-Edwards); D, stented porcine bioprosthesis (Medtronic Mosaic); E, stented pericardial bioprosthesis (Carpentier-Edwards Magna); F, stentless porcine bioprosthesis (Medtronic Freestyle); G, percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); H, self-expandable percutaneous bioprosthesis (CoreValve).**
**Adapted from: (65)**

The ideal valve substitute should simulate the native normal valve characteristics, it should have excellent hemodynamics, long durability, high thromboresistance and excellent implantability. Unfortunately, this does not exist, and each of the available prosthetic valves has limitations.

There are three types of mechanical valves: bileaflet, monoleaflet and caged ball valves (**Fig. 2.9** A, B and C). The criteria in favour of using these valves include:

a) The informed patient desire;

b) No contraindication for long-term anticoagulation therapy or already is on anticoagulation therapy (mechanical valves are more thrombogenic than bioprosthetic valves);
c) Patient is at risk of accelerated bioprosthetisis structural deterioration due to, for example, young age, hyperparathyroidism or renal insufficiency;
d) Patient is less than 65 year of age and has a long-life expectancy;

The design of bioprostheses has the purpose to mimic the anatomy of the native aortic valve, there also are three main types: stented (**Fig. 2.9** D and E), stentless (**Fig. 2.9** F) and percutaneous valves (**Fig. 2.9** G and H). Bioprosthesis may be preferred in some situations:

a) The informed patient desire;
b) Anticoagulation therapy not available or contra-indicated;
c) Patient is more than 65 years of age and/or has limited life expectancy (bioprostheses degenerate more rapidly in young age);
d) patients;
e) Patient is a woman of child-bearing age; (65)

Although prosthetic valves bring many advantages to patients, they have a few but severe adverse effects. The prosthesis obviously predisposes to device related infections, specifically endocarditis. (64)

Early prosthetic valve endocarditis (PVE), can be caused by intraoperative contamination of the valve during implantation. And it can also be caused by hematogenous seeding usually due to another nosocomial infection has a consequence of heavy use of invasive devices, especially intravascular and urinary catheters, in the early postoperative period. In late PVE, pathogen's sites of entry are similar to those in native valve endocarditis, they are mostly community acquired. (1)

Valves made of metal and pyrolytic carbon only allow adherence of microorganisms in the presence of thrombotic material. Adhesion of the bacteria on the injured valvular surface, due to mechanical or inflammatory lesions, is completed in a few minutes during a transient bacteremia. Most infections in mechanical valves begin at the interface between the endocardium of the annulus and the valve sewing ring or at a thrombotic lesion near to the flow recirculation areas. (66) Inflammatory periprosthetic leaks, ring abscesses, and invasion of the infective process into the adjacent tissue are common findings. (64)

In contrast, bioprosthetic valves infections are more likely to begin on the valve structure itself. Pathogenetic mechanism is similar to that of native valves and it is generally limited to the body of leaflets/cusps, causing rupture, perforation and vegetations. (66)

Within the first 12 months after surgery (early PVE) the most common infecting organisms are nosocomial pathogens, like S. aureus, coagulase-negative staphylococci and fungi. Pathogens associated with native-valve endocarditis, such as streptococci and the HACEK (*Haemophilus spp, Actinobacillus actinomycetemcommitans, Cardiobacterium hominis, Eikenella corrodens, and Kingenella spp*) organisms are more related to late PVE.

Aerobic Gram-negative bacilli and fungi appear to be associated with worse outcomes, and streptococci with a much lower mortality. (1)

Risk factors associated with PVE have been identified in several studies (**Table 2.10**). Male gender, black race and previous native valve endocarditis were host factors correlated with these infections. (67)

It has been found that preoperative NYHA (New York Heart Association) functional class III/IV was significantly associated with PVE, which means that patients who undergo surgery earlier have a lower risk. Patients in advanced functional classes are more debilitated and have lower cardiac and metabolic reserves leading to lowered resistance to pathologic organisms. (68)

Alcohol consumption and smoking are also significant determinants of PVE. The higher risk of periodontal disease and/or of postoperative complications and a longer postoperative hospitalization related to subclinical impairment of cardiac function, immune status, and homeostasis, are the reasons behind this. (68) (69)

**Table 2.10 Risk Factors for PVE**

| Non-Modifiable Factors | Modifiable Factors | References |
|---|---|---|
| Male sex | Smoking | (67) (68) (69) |
| Black race | Alcohol consumption | |
| Previous Native Valve Endocarditis | NYHA Functional Class III/IV at time of surgery | |
| Gastrointestinal bleeding | Longer CPB (cardio-pulmonary bypass) time | |
| Skin infections or Wounds | Indwelling medical devices (mainly intravascular) | |

# 3. Infection Management

The most effective treatment in most situations is the replacement or removal of the infected medical device, and systemic antibiotic and/or antifungal therapy.

In patients that can't have surgery, the only option is a long-term antimicrobial suppressive therapy, and salvage rates are highest with early diagnosis.

The antibiotic therapies recommendations for the management of these infections are mostly influenced by empiric observations and usually involve the use of combination regimens over extended periods. In many instances, the preferred treatment options, have emerge through cross-study comparisons of cure rates and other clinical outcomes obtained for particular treatment courses. (70)

## 3.1 Catheter-associated Urinary Tract Infections

According to current evidence, systematic antibiotic treatment is not indicated in asymptomatic catheter-associated bacteriuria, except in the following circumstances:

a) Before urologic surgery or implantation of prostheses;
b) In pregnancy;
c) In patients who have a high risk of serious infectious complications;
d) For infections with strains causing a high incidence of bacteraemia, such as Serratia marcescens; (71)

Systematic antibiotic treatment should only be administered in symptomatic cases. (72) The treatment is started empirically with broadspectrum antibiotics according to local susceptibility patterns, and then initiated targeted therapy according to urine culture results. (71)

The use of the urinary catheter should always be discontinued as soon as appropriate (73), when it's not possible the catheter should be replaced before starting antimicrobial therapy, if it has been in place for more than 1 week. (71)

A urinary fluoroquinolone, such as ciprofloxacin or levofloxacin or a broad-spectrum cephalosporin such as ceftriaxone or cefepime may be used to treat patients with mild to moderate illness without alterations in mental or hemodynamic status.
Piperacillin-tazobactam or a carbapenem should be considered if the patient has evidence of pyelonephritis or urosepsis. And when the urine Gram stain shows gram-positive cocci (most likely enterococci or staphylococci), vancomycin treatment is reasonable. (74) Moxifloxacin should be avoided for the treatment of CAUTI because of uncertainty about the effective concentrations in urine.

Regarding the duration of treatment, a 7-14-day regimen is recommended in most cases, whether the patient remain catheterized or not. A 3-day regimen which is used in uncomplicated UTI, can be used in younger woman with mild CAUTI after the catheter removal. (73)

## 3.2 Catheter-related Bloodstream Infection

After blood cultures are obtained, empiric antimicrobial treatment should be initiated. The definitive therapy is then tailored to the pathogen identified and the susceptibilities of that organism (**Table 3.1**). (75)

Empirical antibiotics should cover methicillin resistant staphylococci, in health care settings with a high prevalence of these pathogens, using vancomycin or alternative agents like daptomycin, when a predominance of MRSA isolates have vancomycin MIC (minimum inhibitory concentration) values of 12 mg/mL. Linezolid is not recommended to be used in empirical therapy. The regimen should also cover gram-negative bacilli, using for this purpose a fourth-generation cephalosporin, carbapenem, or b-lactam/b-lactamase combination, with or without an aminoglycoside.

When CRBI is suspected in neutropenic patients, severely ill patients with sepsis or colonized with MDR gram-negative bacilli (i.e.: P. aeruginosa) patients, an empirical combination antibiotic for those pathogens should be used.

For empirical therapy in suspected CRBSI involving femoral catheters in critically ill patients, the antimicrobial regimen should also cover Candida species, using echinocandin or, for selected patients, fluconazole. (76)

**Table 3.1 Intravenous antimicrobial treatment of CRBSI, according to specific pathogen isolated**

| | Pathogen | Preferred Antimicrobial Agent | |
|---|---|---|---|
| | *S. aureus* | Methicillin susceptible | Penicillinase-resistant **penicillin**: Nafcillin or Oxacillin |
| | | Methicillin resistant | Vancomycin |
| | Coagulase-negative staphylococci | Methicillin susceptible | Penicillinase-resistant **penicillin**: Nafcillin or Oxacillin |
| | | Methicillin resistant | Vancomycin |
| | Enterococcus faecalis/Enterococcus faecium | Ampicillin susceptible | Ampicillin or Penicillin with or without aminoglycoside |
| | | Ampicillin resistant, Vancomycin susceptible | Vancomycin with or without aminoglycoside |
| | | Ampicillin resistant, Vancomycin resistant | Linezolid or Daptomycin |
| Gram-negative bacilli | *E. coli* and Klebsiella species | ESBL negative | Third-generation **cephalosporin**: Ceftriaxone |
| | | ESBL positive | **Carbapenem**: Ertapenem, Imipenem, Meropenem or Doripenem |
| | *P. aeruginosa* | Fourth-generation **cephalosporin** (Cefepime) or **carbapenem** (Imipenem, Meropenem) or Piperacillin and Tazobactam with or without **aminoglycoside** | |
| | Candida species | Echinocandin or Fluconazole if organism is susceptible | |

Adapted from: (75)

In most of confirmed CRBI, the removal of the catheter is recommended, however there are some circumstances in which this is not possible. Either replacing the catheter in another location is not possible, or the removal carries prohibitive risk and the benefits of the salvage outweigh the risks of removal. (75) Therefore there are unique aspects

of treating patients who have different types of catheters and are infected with different type of microorganisms.

When patients have an uncomplicated short-term central venous catheter or arterial catheter–related bloodstream infection, the catheter is removed and the patient is treated with systemic antimicrobial agents. If the pathogen responsible is a coagulase-negative Staphylococcus (CNS) the treatment should last 5-7 days, ≥14 days when S. aureus is identified, 7-14 days in Enterococcus or Gram bacilli related cases, and 14 days (after the first negative blood culture) in Candida spp cases. If the catheter is retained in CNS infections, the patient should be treated with systemic antibiotics and antibiotic lock therapy for 10-14 days.

In complicated infections like suppurative thrombophlebitis, endocarditis and osteomyelitis the catheter is removed and systemic antibiotic treatment lasts for 4-6 weeks in the first two situations, and 6-8 weeks in adults with osteomyelitis.

On the other hand, in patients with an uncomplicated long-term central venous catheter or port-related bloodstream infection, the catheter may be retained in CNS Enterococcus and Gram negative bacilli using systemic antibiotics and antibiotic lock therapy. This treatment should last 10-14 days in CNS infections and Gram negative bacilli, and 7-14 days in Enterococcus infections. But if there is clinical deterioration, persisting or relapsing bacteremia, then the catheter should be removed.

S. aureus and Candida spp are an exception, the catheter shouldn’t be retained and the patient needs to be treated with antibiotics for 4-6 weeks in the first case and with antifungal therapy for 14 days (after the first negative blood culture) in the latter.

Regarding complicated infections there are two situations. Tunnel infection or port abscess, where the remove of the catheter is needed and there is treatment with antibiotics for 7-10 days. And septic thrombosis, endocarditis or osteomyelitis, where the removal of the catheter is also needed and treatment with systemic antibiotics for last for 4-6 weeks in the first two conditions and 6-8 weeks in osteomyelitis in adults.

Antibiotic lock therapy is used to salvage the catheter, and is indicated in patients with CRBI involving long-term catheters with no signs of exit site or tunnel infection.

It involves placing a high concentration of an antibiotic to which the pathogen is susceptible in the catheter lumen. However, this therapy doesn't always succeeds, it depends on the site of infection (e.g., tunnel or pocket infections are unresponsive) and on the organism causing the infection (e.g., CNS are responsive but S. aureus is not). (76)

## 3.3 Ventilator-associated Pneumonia

The delayed therapy in VAP cases increases mortality, making the choice of empirical treatment crucial and it should start immediate after microbiological sampling. When VAP is suspected, therapy should always be based on knowledge of local pathogens and the patient risk factors, but it is recommended to include coverage for S. aureus, methicillin susceptible or methicillin resistant (vancomycin or linezolid), P. aeruginosa, and other gram-negative bacilli. (77)

Once culture results are available, a modification of the initial regimen with a de-escalation of antibiotics strategy takes place. The response to treatment should also be assessed after 72h. (78)

IDSA most recent guidelines advise de use of vancomycin or linezolid when MRSA pathogen is isolated. Regarding P. aeruginosa no specific antibiotic has been recommended, the choice of therapy should be based upon antibiotic susceptibly testing results. The reason behind this, is that 2/3 of patients with VAP caused by this pathogen have antibiotic resistance and this resistance is widely variable. The strategy for ESBL-producing gram-negative microorganism is the same, antibiotic choice should have in consideration both susceptibility testes and patient specific factors. When Acinetobacter species are identified, treatment with carbapenem or ampicillin/sulbactam is used, if it's only sensitive to polymyxins then it should be used polymyxin B or colistin.

When a patient is on an appropriate regimen and not infected by a mutridrugresistant microorganism or P. aeruginosa, short therapy for 7 days is appropriate. A short-course antibiotic regimen decreases antibiotic exposure, side effects and resistance without increasing recurrent disease or mortality. (77)

## 3.4 Peritoneal Dialysis Peritonitis

Much like other infections as soon as is suspected that the patient has PD peritonitis and after the microbiological specimens have been obtain for tests, empirical antibiotic therapy should be initiated.

It is recommended that the empirical antibiotic regimen covers both gram-positive (vancomycin) and gram-negative (third-generation cephalosporin or an aminoglycoside) microorganisms.

The antibiotics favoured route of administration is intraperitoneal (IP), unless the patient has features of systemic sepsis.

It is suggested by the International Society for Peritoneal Dialysis, that an infection by CNS should be treated with IP cephalosporins or vancomycin, depending on antimicrobial susceptibility, for a period of 2 weeks. For enterococcal peritonitis the recommended treatment IP vancomycin for 3 weeks. In case of *S. aureus* peritonitis, if it is methicillin-sensitive, a first-generation cephalosporin is the drug of choice, but if the isolate is methicillin-resistant, the drug of choice is IP vancomycin and in both cases the treatment lasts 3 weeks. And Pseudomonas peritonitis is treated with 2 antibiotics to which the organism is sensitive but that have different mechanism of action (e.g. IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks.

PD catheters are removed in refractory, relapsing, or fungal peritonitis and the re-insertion should be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms. The procedure should be done by laparoscopic or mini-laparotomy approach. (79)

## 3.5 Cardiac Device-related Infections

Prompt removal of all the cardiac device hardware and a prolonged course of intravenous antibiotics is the main strategy when there's a confirmation of CDI regardless of it is systemic or localised in the pocket. But there exists cases of minor incisional abscesses, a few days after implantation, where a course of antibiotics and a follow-up can be sufficient. (80)

Because most of the infections are due to staphylococcal species, and some of them may be oxacillin resistant, the empirical antibiotic coverage should consist of vancomycin until microbiological results are known.

If the patient has an infection due to oxacillin-susceptible staphylococcal strains, then it can be given cefazolin or nafcillin alone with discontinuation of vancomycin. However, if the cause is oxacillin-resistant staphylococci or the patient is not a candidate for β-lactam antibiotic therapy, vancomycin treatment is continued. In vitro susceptibility testing should be used to identify the best treatment in the minority of patients with non-staphylococcal infection. (62)

Generally, the recommended duration of treatment is 10-14 days after a pocket infection, 14 days for bloodstream infection, and 4-6 weeks for endocarditis. (80)

Before the system extraction, a plan for re-implantation is designed. The cardiac device necessity must be re-evaluated, because some problems may have been resolved, and some other indications for more complex device treatment may have been developed. If the re-implantation is necessary, and if it is possible, it should be done on the opposite side of the chest, or via transiliac approach. The timing has to be individualised, with careful attention to an adequate period of antibiotic therapy. (80,81)

## 3.6 Prosthetic Valve Endocarditis

Until a pathogen is identified, the antimicrobial therapy is empirical. The selection of an optimal empiric regimen is based on factors that relate to patient characteristics, prior antimicrobial exposures and microbiological findings, and epidemiological features.
When the microorganism is finally isolated and the susceptibility results are obtained, the regimen is revised. (82)

The European Society of Cardiology proposes different antibiotics for empiric treatment early and late PV endocarditis, because there are different pathogens associated with each type of infection. Late PVE regimens should cover staphylococci, streptococci and enterococci, with ampicillin, (flu)cloxacillin or oxacillin and gentamicin or for penicillin-allergic patients, vancomycin and gentamicin. Early PVE regimens should cover methicillin-resistant staphylococci, enterococci and, ideally, non-HACEK Gram-negative pathogens, with vancomycin, gentamicin and rifampin.

If methicillin-susceptible staphylococci are responsible for the infection (flu)cloxacillin or oxacillin with Rifampin and Gentamicin are used in the treatment. For penicillin-allergic patients and methicillin-resistant staphylococci, vancomycin with rifampin and gentamicin are recommended.
Enterococci are highly resistant microorganism, and eradication requires prolonged administration (up to 6 weeks) of synergistic bactericidal combinations of two cell wall inhibitors (ampicillin plus ceftriaxone, which synergize by inhibiting complementary PBPs) or one cell wall inhibitor with aminoglycosides.
Since some HACEK-group bacilli produce beta-lactamases, the standard treatment is ceftriaxone for 6 weeks in PVE. If they do not produce beta-lactamase, ampicillin plus gentamicin for 4–6 weeks is an option.
For non-HACEK Gram-negative bacteria, the suggested treatment is early surgery and long-term (at least 6 weeks) therapy with bactericidal combinations of beta lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole.

Surgery is recommended for PVE in some high-risk subgroups, like PVE complicated by hearth failure, severe prosthetic dysfunction, abscess or persistent fever. Emergency surgery is indicated in cases where refractory congestive heart failure leading to pulmonary oedema or shock is present. On the other hand, patients with uncomplicated non-staphylococcal and non-fungal late PVE can be managed conservatively with close follow-up. (83)

# 4. Infection Prevention

## 4.1 Nontechnological Recommendations

Training and education are an important part in prevention, and are critical for the people who are responsible for the use the devices, patient care and infection control. However, devices are often introduced into the healthcare environment without the proper orientation and training. It's often difficult to find the time for training the staff when the workload is overwhelming, so it is important that a training program is well conceived and that the institution/hospital provides the resources to implement it.

It's also important to educate non-patients (visitors and the public), who can still influence device-related transmission of infections, about the importance of the role of personal protective equipment, hand hygiene, and staying away from healthcare facilities when they're sick.

Hand hygiene is the most effective preventive strategy according to CDC, but the compliance with hand hygiene practices among healthcare workers is still very low. (84) Routine hand washing before and after contact with a patient, performing invasive procedures, touching wounds and contact with inanimate sources (such as devices) that are potentially contaminated with microorganisms, can prevent many nosocomial infections.

WHO and CDC recommend that the healthcare facility should have policies and procedures for handwashing, and that these will vary according the patient risk assessment:

a) Routine care (minimal risk): handwashing with non-antiseptic soap or quick hygienic hand disinfection (by rubbing) with alcoholic solution;
b) Antiseptic hand cleaning (moderate risk)-aseptic care of infected patients: hygienic handwashing with antiseptic soap following manufacturer's instructions (e.g. one minute) or quick hygienic hand disinfection: as previously;

c) Surgical scrub (surgical care/high risk): surgical hand and forearm washing with antiseptic soap and sufficient time and duration of contact (3–5 minutes) or surgical hand and forearm disinfection: simple hand wash and drying followed by two applications of hand disinfectant, then rub to dry for the duration of contact defined by the product; (3)

Cleaning, disinfecting, and sterilization of instruments, devices, equipment and surfaces also have a huge impact on reducing the transmission of infection. Establishing protocols based on standards and regulatory criteria, selecting the right products and ongoing monitoring is recommended. Surveillance programs should be developed based on the statistical risk of contamination. The routine surveillance (testing) of items that are determined to be ready for patient, can prevent transmission and help the identification of sources of contamination in the facility. Practices should be proactive and preventive, rather than reactive.

Another factor with a high potential impact to reduce HAIs is the poor device management at point of use, clinicians using medical devices (e.g. surgical instruments or diagnostic equipment) have an obligation to maintain cleanliness when the device is in use and then prepare it properly for return to the processing department.

Many more steps can be taken in consideration when designing a prevention program, but the success of the program implementation depends on the whole healthcare facility being on board, it is impossible to implement prevention strategies that are not actively supported. Preventing adverse events of all types requires everyone to be vigilant and to speak up when they observe something troubling and there must be accountability for HAIs at all staffing levels within a facility. Without support and enforcement, policies and strategies have little effect. (84)

## 4.2 Medical Device Design

Although hand washing, aseptic techniques, control of environment and devices sterility and perioperative antibiotic prophylaxis are necessary to prevent medical device-associated infections, these aren't the only strategies available.

A promising way of preventing the infection is the development of medical devices with surfaces or materials that have an action against the microorganisms and the biofilm formation. It has been developed a very broad variety of approaches to achieve anti-infective biomaterials. (85,86)

The bulk material of the medical device properties determines the mechanical behaviour, but the biocompatible/bioactive coating increases the performance of functionalized surfaces that couldn't be achieved by just utilizing the bulk materials and can provide antibacterial properties.

There are three major strategies for designing antibacterial coatings: anti-adhesion/anti-fouling, antibacterial agent release and contact-killing (**Fig. 4.1**) (87)

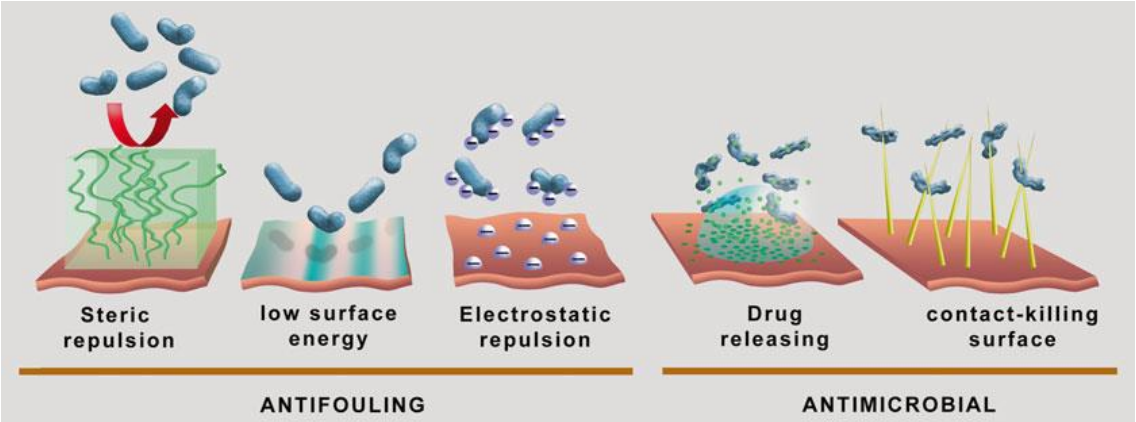


**Fig. 4.1 Classes of antifouling or antimicrobial polymers.**
**Adapted from: (88)**

### 4.2.1 Anti-adhesion/Anti-fouling

The earliest step in the pathogenesis of medical device related infections is bacterial adhesion, so numerous strategies to modify surfaces to be anti-fouling to bacteria have been developed. Since the microbial surfaces are mainly hydrophobic and negatively charged, the anti-fouling polymers should be either: hydrophilic, negatively charged or with low surface free energy, in order to repel microbes. (88)

A lot of hydrophilic polymers have shown promising anti-fouling properties, improving wettability and lubricity, like PEG, polyamides and polysaccharides. However, their hydration layer is formed by hydrogen bonds that are easily breakable and reformed, so these polymers may lose the anti-fouling properties upon a change in surface hydration. Zwitterionic polymers, on the other hand, bind more strongly and are more stable due to electrostatically induced hydration, in most conditions they are quite robust when compared to hydrophilic antifouling surfaces. (89)

Heparin and albumin are negative charged polymers that reduce bacterial adhesion onto medical devices surfaces, due to electrostatic repulsion. And the most known low surface energy polymers are silicone elastomers and fluoropolymers. (88)

### 4.2.2 Release-Based Antibacterial Coatings

The antibacterial activity of the release-based coatings is achieved with the discharge of antibacterial compounds over time, killing both adhered and adjacent planktonic bacteria.

The release of the antibacterial substances can happen in three different ways: diffusion into the aqueous medium, erosion/degradation, or hydrolysis of covalent bonds. The direct elution from the material surface, delivers a high antibacterial agent concentration locally, without causing systemic toxicity or ecotoxicity, and minimizes the development of resistance. But, since the coatings have limited reservoirs of antibacterial agents, their action is only temporary.

A lot of methods to deliver these compounds have been developed over the years; the oldest and most common is simple impregnation, by soaking a porous material or coating with the desired antibacterial agent, leading to a fast release due to the lack of a bonding mechanism.

Since then delivery systems have evolved and now include carrier materials, the most frequently used are poly (methacrylic acid) (PMMA), polyacrylic acid (PAA), poly (lactic-co-glycolic acid) (PLGA), hydroxyapatite, polyurethane (PU), a hyaluronic acid, and chitosan. Hydrogels, ceramics, and plasma-deposited polymers are also known to be suitable carrier coatings for the delivery of antibacterial compounds.

An even more recent approach is the use of polyelectrolyte multilayers (PEMs), they are nanostructured polymeric systems that can be formed layer-by-layer (LbL) deposition, with alternating layers with opposite charges. The antibacterial agents can either be trapped between the layers or constitute an integral part of the coating, by replacing one of the charged species. This is one of the most successful, simple, versatile and low cost method to deliver antibacterial compounds in coatings.

In the end, the choice of materials will always depend on the compatibility between scaffold and antibacterial agent, the necessary matrix functionalities and desired release mode. (87)

A broad range of antibacterial substances have been used in these delivery systems, from antibiotics to antibacterial peptides (magainin and nisin) and other notorious antimicrobial molecules like triclosan, quaternary ammonium compounds, chlorhexidine and benzalkonium chloride. Even metals like silver, zinc, copper, gallium and selenium, enzymes (lysozyme and acylase), or nitric oxide and reactive oxygen species (ROS) can also be incorporated in these coatings. (86)

### 4.2.3 Contact-Killing

The disadvantage of the release-based antibacterial coatings is that they show a high-burst release, so contact-killing coatings have been developed to resolve this issue. In this method, antimicrobial compounds are covalently bonded to the material surfaces by polymers. They have a long-term antimicrobial activity and don't promote the development of bacterial resistance.

Most of these coatings have in their composition, either cationic compounds, like quaternary ammonium compounds (QACs), chitosan and antimicrobial peptides (AMPs) or enzymes. The bacteria are killed upon contact due to severe membrane disruption by the attached antibacterial compounds, this can either happen because of physical lysing or charge disruption. (87,90)

# 5. Conclusion

HAIs are a major public health issue, leading to significant mortality and having a high socioeconomic impact. Most of these infections are related to medical devices, and although the use of these devices may come with a risk, they are in many cases crucial for the management of an illness or even for the survival of the patient, so it is necessary to develop efficient DAIs prevention and treatment strategies.

It is known that the pathogens that are responsible for these infections have many particularities, the fact that they live in communities like biofilms, which helps them to develop resistance to antimicrobial agents, makes them unpredictable. And for this reason, the training of health-care personnel must be continuous and up to date, and the research and development of new antimicrobial substances and new technologies for prevention will always be areas of ongoing research and growth.

The key to succeed in the fight against DAIs relies on multidisciplinary teams, with tight collaborations of experts in medicine, pharmaceutical sciences, medical microbiology, pharmacology and biomaterials and the involvement of medical device industries.

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